4. (**Reiterated**) The protein of claim 1, wherein the protein further comprises a hydrophobic moiety substituted for, or appended to, the C-terminal amino acid.

5. (**Reiterated**) The protein of claim 1, wherein the protein is an extracellular signaling protein.

6. (**Reiterated**) The protein of claim 1, wherein the N-terminal amino acid is a functional derivative of a cysteine.

7. (**Reiterated**) The protein of claim 1, wherein the protein is modified at both the N-terminal amino acid and the C-terminal amino acid.

8. (**Reiterated**) The protein of claims 4 or 7, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one internal amino acid.

9. (**Reiterated**) The protein of claim 1, wherein the protein has a hydrophobic moiety substituted for, or appended to, at least one amino acid intermediate to the N-terminal and C-terminal amino acids.

10. (**Reiterated**) The protein of claim 3, wherein the lipid moiety is a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

14. (**Reiterated**) The protein of claim 1, further comprising a vesicle in contact with the hydrophobic moiety.

15. (**Reiterated**) The protein of claim 14, wherein the vesicle is selected from a cell membrane, a micelle, and a liposome.

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28. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal thioproline group, said group formed by reacting an aldehyde with an N-terminal cysteine of the protein, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

29. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal amide group, said group formed by reacting a fatty acid thioester with an N-terminal cysteine of the protein, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C3 Cont'd

30. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal maleimide group, said N-terminal maleimide group formed by reacting a maleimide group with the N-terminal cysteine of the protein, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

31. (**Reiterated**) The isolated protein of claims 28, 29 or 30, wherein the C-terminal amino acid of the protein is modified with a hydrophobic moiety.

C4

40. (**Amended**) A method for modifying a physico-chemical property of a protein, comprising introducing at least one hydrophobic moiety to an N-terminal cysteine of the protein or to a functional equivalent of the N-terminal cysteine, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

41. (**Reiterated**) The method of claim 40, further comprising contacting the hydrophobic moiety with a vesicle.

42. (**Reiterated**) The method of claim 40, wherein the hydrophobic moiety is either a lipid moiety selected from saturated and an unsaturated fatty acids having between 2 and 24 carbon atoms or is a hydrophobic protein.

46. (**Reiterated**) The method of claim 41, wherein the step of contacting comprises contacting with a vesicle selected from a cell membrane, liposome and micelle.

48. (**Reiterated**) A modified protein, produced by the method of claim 40.

C5

50. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid thioester to

C5 cont'd

form an amide, wherein such modification enhances the protein's biological activity, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C6

53. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a maleimide group, wherein such modification enhances the protein's biological activity, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C7

56. (**Amended**) A method for modifying a protein that binds to an extracellular receptor, comprising appending a hydrophobic peptide to the protein, wherein the protein has a biological activity and the hydrophobic peptide enhances the biological activity, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

57. (**Reiterated**) The method of claim 56, wherein the hydrophobic peptide is appended to an amino acid of the protein selected from the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid, and the C-terminal amino acid, and combinations of the foregoing.

63. (**Reiterated**) The method of claim 57, wherein the step of appending comprises replacing at least the N- terminal amino acid of the protein with at least one hydrophobic amino acid.

64. (**Reiterated**) The method of claim 63, wherein the at least one hydrophobic amino acid is a plurality of isoleucine residues.

65. (**Reiterated**) The method of claim 63, further comprising chemically modifying at least one of the isoleucine residues.

C8

66. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal acetamide group, said group formed by reacting a substituted acetamide with an N-terminal

cysteine of the protein, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C8 cont'd

67. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal thiomorpholine group, said group formed by reacting a haloketone group with an N-terminal cysteine of the protein, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C9

68. (**Thrice Amended**) A method for modifying a protein that binds to an extracellular domain of a cell membrane-associated receptor and contains an N-terminal cysteine, comprising reacting the N-terminal cysteine with a substituted acetamide group, wherein said protein has a biological activity, and the acetamide group enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C10

71. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a haloketone group, wherein such modification enhances the protein's biological activity, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

C11

87. (**Twice Amended**) A method for modifying a protein that binds an extracellular domain of a cell membrane-associated receptor, comprising treating the protein with an active thioester under conditions sufficient to acylate the protein, wherein said protein has a biological activity, and acylation of the protein enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

88. (**Reiterated**) The method of claim 87, wherein the protein is acylated at an amino acid selected from the N-terminal amino acid, the C-terminal amino acid, an amino acid intermediate between the N-terminal amino acid and the C-terminal amino acid, and combinations of the foregoing.

89. (**Twice Amended**) A method for modifying a protein that binds an extracellular domain of a cell membrane-associated receptor and contains an N-terminal cysteine, comprising reacting C12 the N-terminal cysteine with a fatty acid active thioester to form an amide, wherein said protein has a biological activity, and the modification enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

93. (**Twice Amended**) An isolated polypeptide ligand for a receptor, which receptor includes C13 an extracellular domain and which receptor is membrane-associated, wherein the ligand comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched, and wherein said ligand is covalently attached to a hydrophobic moiety that enhances the biological activity of the ligand relative to the biological activity of the ligand in the absence of the hydrophobic moiety.

94. (**Reiterated**) The ligand of claim 93, wherein the hydrophobic moiety is a peptide comprising at least one hydrophobic amino acid.

95. (**Reiterated**) The ligand of claim 93, wherein the hydrophobic moiety is a lipid.

96. (**Reiterated**) The ligand of claim 93, wherein the protein further comprises a hydrophobic moiety substituted for, or appended to, the C-terminal amino acid.

97. (**Reiterated**) The ligand of claim 93, wherein the protein is an extracellular signaling protein.

98. (**Reiterated**) The ligand of claim 93, wherein the N-terminal amino acid is a functional derivative of a cysteine.

99. (**Reiterated**) The ligand of claim 93, wherein the ligand is modified at both the N-terminal amino acid and the C-terminal amino acid.

100. (**Reiterated**) The ligand of claim 96 or 99, wherein the ligand has a hydrophobic moiety substituted for, or appended to, at least one internal amino acid.

101. (**Reiterated**) The ligand of claim 93, wherein the ligand has a hydrophobic moiety substituted for, or appended to, at least one amino acid intermediate to the N-terminal and C-terminal amino acids.

102. (**Reiterated**) The ligand of claim 95, wherein the lipid moiety is a fatty acid selected from saturated and unsaturated fatty acids having between 2 and 24 carbon atoms.

103. (**Reiterated**) The ligand of claim 93, further comprising a vesicle in contact with the hydrophobic moiety.

104. (**Reiterated**) The ligand of claim 103, wherein the vesicle is selected from a cell membrane, a micelle, and a liposome.

Please add the following new claims:

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105. (**NEW**) The protein of claim 1, wherein said protein binds patched and comprises an amino acid sequence at least 90% identical to any of SEQ ID NOs: 1-4.

106. (**NEW**) The protein of claim 105, wherein said protein comprises an amino acid sequence identical to any of SEQ ID NOs: 1-4.

107. (**NEW**) The protein of any of claims 28, 29 or 30, wherein said protein binds patched and comprises an amino acid sequence at least 90% identical to any of SEQ ID NOs: 1-4.

108. (**NEW**) The protein of claim 107, wherein said protein comprises an amino acid sequence identical to any of SEQ ID NOs: 1-4.

109. (**NEW**) The method of claim 40, wherein said protein binds patched and comprises an amino acid sequence at least 90% identical to any of SEQ ID NOs: 1-4.

C14 Cont'd

110. (**NEW**) The method of claim 109, wherein said protein comprises an amino acid sequence identical to any of SEQ ID NOs: 1-4.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. (**Thrice Amended**) An isolated protein comprising an N-terminal amino acid and a C-terminal amino acid, wherein the protein comprises an amino acid sequence selected from:

(a) an amino acid sequence with an N-terminal cysteine that is appended with at least one hydrophobic moiety;

(b) an amino acid sequence with an N-terminal amino acid that is not a cysteine appended with at least one hydrophobic moiety; and

(c) an amino acid sequence with at least one hydrophobic moiety substituted for the N-terminal amino acid,

wherein the protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched, and wherein said hydrophobic moiety enhances a biological activity of the protein ~~, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

28. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal thioproline group, said group formed by reacting an aldehyde with an N-terminal cysteine of the protein, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched ~~, in the absence of the thioproline group, binds to a receptor or coreceptor, and the thioproline group does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

29. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal amide group, said group formed by reacting a fatty acid thioester with an N-terminal cysteine of the

protein, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the amide group, binds to a receptor or coreceptor, and the amide group does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

30. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal maleimide group, said N-terminal maleimide group formed by reacting a maleimide group with the N-terminal cysteine of the protein, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the maleimide group, binds to a receptor or coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

40. (**Amended**) A method for modifying a physico-chemical property of a protein, comprising introducing at least one hydrophobic moiety to an N-terminal cysteine of the protein or to a functional equivalent of the N-terminal cysteine, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the hydrophobic moiety, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

50. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid thioester to form an amide, wherein such modification enhances the protein's biological activity, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the modification, binds to a receptor or coreceptor, and the modification does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

53. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a maleimide group, wherein such modification enhances the protein's biological activity, wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched ~~wherein the protein, in the absence of the maleimide group, binds to a receptor or~~

~~coreceptor, and the maleimide group does not substantially affect binding affinity of the protein to the receptor or coreceptor, and wherein such modification enhances the protein's biological activity~~.

56. (**Amended**) A method for modifying a protein that binds to an extracellular receptor, comprising appending a hydrophobic peptide to the protein, wherein the protein has a biological activity and the hydrophobic peptide enhances the biological activity, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

66. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal acetamide group, said group formed by reacting a substituted acetamide with an N-terminal cysteine of the protein, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the acetamide group, binds to a receptor or coreceptor, and the hydrophobic moiety does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

67. (**Amended**) An isolated protein having a C-terminal amino acid and an N-terminal thiomorpholine group, said group formed by reacting a haloketone group with an N-terminal cysteine of the protein, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the thiomorpholine group, binds to a receptor or coreceptor, and the thiomorpholine group does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

68. (**Thrice Amended**) A method for modifying a protein that binds to an extracellular domain of a cell membrane-associated receptor and contains an N-terminal cysteine, comprising reacting the N-terminal cysteine with a substituted acetamide group, ~~wherein such modification enhances the protein's biological activity,~~ wherein ~~the~~ said protein has a biological activity, and the acetamide group enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

71. (**Amended**) A method for modifying a protein having a biological activity and containing an N-terminal cysteine, comprising reacting the N-terminal cysteine with a haloketone group, wherein such modification enhances the protein's biological activity, wherein ~~the~~ said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched~~, in the absence of the haloketone group, binds to a receptor or coreceptor, and the haloketone group does not substantially affect binding affinity of the protein to the receptor or coreceptor~~.

87. (**Twice Amended**) A method for modifying a protein that binds an extracellular domain of a cell membrane-associated receptor, comprising treating the protein with an active thioester under conditions sufficient to acylate the protein, wherein ~~the~~ said protein has a biological activity, and acylation of the protein enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

89. (**Twice Amended**) A method for modifying a protein that binds an extracellular domain of a cell membrane-associated receptor and contains an N-terminal cysteine, comprising reacting the N-terminal cysteine with a fatty acid active thioester to form an amide, wherein ~~the~~ said protein has a biological activity, and the modification enhances the biological activity of the protein, and wherein said protein comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched.

93. (**Twice Amended**) An isolated polypeptide ligand for a receptor, which receptor includes an extracellular domain and which receptor is membrane-associated, wherein the ligand comprises an amino acid sequence at least 80% identical to any of SEQ ID NOs: 1-4 and binds patched, and wherein said ligand is covalently attached to a hydrophobic moiety that enhances the biological activity of the ligand relative to the biological activity of the ligand in the absence of the hydrophobic moiety.